Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

***Current Policy Effective Date: 3/1/25**
(See policy history boxes for previous effective dates)

Title: Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric Disorders

Description/Background

INTRAVENOUS ANESTHETIC AGENTS

Courses of intravenous (IV) anesthetic agents may be given in the inpatient or outpatient setting as part of a pain management program, with the infusion of a subanesthetic dose preceded by a bolus infusion to achieve desired blood levels sooner. Treatment protocols for the initial cycle may include infusion of subanesthetic doses of 1 to 6 hours for up to 10 days.

Ketamine

Ketamine is an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor and a dissociative anesthetic. It is the sole anesthetic agent approved for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Respiratory depression may occur with over-dosage or too rapid a rate of administration of ketamine; it should be used by or under the direction of physicians experienced in administering general anesthetics. Ketamine is a schedule III controlled substance. Psychological manifestations vary in severity from pleasant dream-like states to hallucinations and delirium, and can be accompanied by confusion, excitement, aggression, or irrational behavior. The occurrence of adverse events (AEs) with IV anesthetics may be reduced by the careful titration of subanesthetic doses. However, the potential benefits of pain control must be carefully weighed against the potential for serious, harmful AEs.

Lidocaine

Lidocaine, which prevents neural depolarization through effects on voltage-dependent sodium channels, is also used systemically for the treatment of arrhythmias. AEs for lidocaine are common, can be mild to moderate, and include general fatigue, somnolence, dizziness, headache, periorbital and extremity numbness and tingling, nausea, vomiting, tremors, and changes in blood pressure and pulse. Severe adverse effects may include arrhythmias, seizures, loss of consciousness, confusion, or even death. Lidocaine should only be given

intravenously to patients with normal conduction on electrocardiography and normal serum electrolyte concentrations to minimize the risk of cardiac arrhythmias.

Indications

IV administration of anesthetic has been reported for various conditions, including chronic pain of neuropathic origin, chronic headache, fibromyalgia, depression, and obsessive-compulsive disorders.

Chronic daily headache is defined as a headache disorder that occurs more than 15 days a month for at least 3 months. Chronic daily headache includes chronic migraine, new daily persistent headache, hemicranias continua, and chronic tension-type headache.

Neuropathic pain is often disproportionate to the extent of the primary triggering injury and may consist of thermal or mechanical allodynia, dysesthesia, and/or hyperalgesia. Allodynia is pain that occurs from a stimulus that normally does not elicit a painful response (e.g., light touch, warmth). Dysesthesia is a constant or ongoing unpleasant or electrical sensation of pain. Hyperalgesia is an exaggerated response to normally painful stimuli. In the latter, symptoms may continue for a period of time that is longer (e.g., ≥6 months) than clinically expected after an illness or injury. It is proposed that chronic neuropathic pain results from peripheral afferent sensitization, neurogenic inflammation, and sympathetic afferent coupling, along with sensitization and functional reorganization of the somatosensory, motor, and autonomic circuits in the central nervous system (CNS). Therefore, treatments focus on reducing activity and desensitizing pain pathways, thought to be mediated through NMDA receptors in the peripheral and CNS. Sympathetic ganglion blocks with lidocaine have been used for a number of years to treat sympathetically maintained chronic pain conditions, such as complex regional pain syndrome (previously known as reflex sympathetic dystrophy). Test infusion of an anesthetic has also been used in treatment planning to assess patient responsiveness to determine whether medications, such as oral mexiletine or oral ketamine, may be effective. A course of IV lidocaine or ketamine, usually at subanesthetic doses, has also been examined. This approach for treating chronic neuropathic pain differs from continuous subcutaneous or IV infusion of anesthetics for the management of chronic pain conditions, such as terminal cancer pain, which are not discussed herein.

Fibromyalgia is a chronic state of widespread pain and tenderness. Although fibromyalgia is generally considered to be a disorder of central pain processing or central sensitization, others have proposed that the nerve stimuli causing pain originates mainly in the muscle, causing both widespread pain and pain on movement. There are focal areas of hyperalgesia, or tender points, which tend to occur at muscle tendon junctions. Biochemical changes that have been associated with fibromyalgia include alterations in NMDA receptors, low levels of serotonin, suppression of dopamine-releasing neurons in the limbic system, dysfunction of the hypothalamic-pituitary-adrenal axis, and elevated substance P levels. Fibromyalgia is typically treated with neuropathic pain medications such as pregabalin, non-narcotic pain relievers, or low doses of antidepressants.

Use of IV ketamine has also been reported for treatment-resistant depression, defined as depression that does not respond adequately to appropriate courses of antidepressant medications. Particularly challenging are patients with treatment-resistant depression with suicidal ideation. Several studies are ongoing to test the efficacy of IV ketamine in patients with suicidal ideation who present to the emergency department.

Regulatory Status

Intravenous (IV) lidocaine systemically is approved by the U.S. Food and Drug Administration (FDA) for the acute treatment of arrhythmias and locally as an anesthetic. IV lidocaine for the treatment of chronic pain is an off-label use.

Ketamine hydrochloride injection is FDA-indicated for diagnostic and surgical procedures that do not require skeletal muscle relaxation, for the induction of anesthesia prior to the administration of other general anesthetic agents, and to supplement low-potency agents, such as nitrous oxide. IV ketamine for the treatment of chronic pain is an off-label use.

Medical Policy Statement

Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the treatment of chronic pain including, but not limited to chronic neuropathic pain, chronic daily headache, and fibromyalgia is considered experimental/investigational. It has not been scientifically demonstrated to improve patient clinical outcomes.

Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the treatment of psychiatric disorders, including but not limited to treatment-resistant depression, obsessive-compulsive disorder, and post-traumatic stress disorder is considered investigational. It has not been scientifically demonstrated to improve patient clinical outcomes.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

96365* 96366* J2001* J3490*

*Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

INTRAVENOUS ANESTHETICS FOR INDIVIDUALS WITH CHRONIC PAIN

Clinical Context and Therapy Purpose

The purpose of a course of intravenous (IV) anesthetics (e.g., lidocaine, ketamine) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with chronic pain syndromes (e.g., complex regional pain syndrome [CRPS], fibromyalgia, headache, neuropathic pain, spinal cord injury).

The following **PICOs** were used to select literature to inform this review

Populations

The relevant population of interest is individuals with chronic pain syndromes (e.g., CRPS, fibromyalgia, headache, neuropathic pain, spinal cord injury).

Interventions

The therapy being considered is a course of IV anesthetics (e.g., lidocaine, ketamine).

Comparators

The following therapy is currently being used to treat chronic pain syndromes: oral pain medication.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- Studies with short-term outcomes (<24 h) were excluded.
- Studies with duplicative or overlapping populations were excluded.

NEUROPATHIC PAIN

Systematic Reviews

A network meta-analysis by Wertli et al (2014) evaluated the efficacy of all agent classes investigated in RCTs and provided a rank order of various substances.[7] Sixteen studies on bisphosphonates, calcitonin, *N*-methyl-d-aspartate analogues, analgesics, vasodilators, steroids, anticonvulsive agents, and radical scavengers were analyzed. Of these, only bisphosphonates, *N*-methyl-d-aspartate analogues (ketamine), and vasodilators showed better long-term pain reduction than placebo. The 2 RCTs on ketamine were reported by Schwartzman et al (2009) (N=19) and Sigtermans et al (2009) (N=60), the latter of which is described below.[8,9]

The same 16 studies were selected by O'Connell et al (2013) in a Cochrane overview of interventions for CRPS, which found low-quality evidence that a course of IV ketamine may be effective for CRPS-related pain; the effects of such a course were not sustained beyond 4 to 11 weeks posttreatment.[10] An update to this Cochrane review similarly found that evidence for use of ketamine for patients with CRPS was of very low certainty; the authors identified moderate-certainty evidence that local sympathetic nerve blockade with lidocaine probably does not reduce pain relative to placebo.[11,]

A qualitative systematic review identified 27 studies evaluating lidocaine infusion for chronic neuropathic pain of varying etiologies, including spinal cord injury, peripheral nerve injury, diabetic neuropathy, post-herpetic neuralgia (PHN), and CRPS.[12,] In the narrative synthesis, the authors noted that evidence for each etiology was insufficient (owing, in part, to heterogeneity, with significant variability in outcome reporting and results) and underpowered, and that no recommendation for lidocaine infusion in these settings could be made.

Randomized Controlled Trials

Tables 1 and 2 summarize the characteristics and results of selected RCTs.

Lidocaine

Several RCTs have been performed using intravenous lidocaine for postherpetic neuralgia (PHN), CRPS, and diabetic neuropathy. These trials have failed to show a durable effect of lidocaine infusion on chronic pain.

Kim et al (2018) published a prospective, randomized, double-blind, placebo-controlled trial evaluating 43 patients with PHN or CRPS who were randomized to lidocaine or placebo (saline) in 4 weekly infusions.[13] The groups did not differ significantly at weeks 1 and 2 in a reduction in pain; however, there were between-group differences after weeks 3 and 4 (respectively, p=0.001 and p=0.009). In the lidocaine-treated group, there was a significantly greater reduction in pain following the final infusion compared with the placebo group (p=0.011). However, this difference in the percentage of pain reduction was not reported at follow-up assessments in 1 and 4 weeks after the final infusion, suggesting only a temporary analgesic effect.

Liu et al (2018) randomized 189 patients with PHN to a single 1 1/2 h infusion of lidocaine with injection of midazolam and granisetron.[14] Patients were also taking pregabalin and oxycodone as needed. The control group received saline with midazolam and granisetron. The study was double-blind with allocation concealment and an independent assessor. Pain scores decreased from baseline in both groups, but there was no significant difference in scores between the lidocaine and placebo groups. However, patients treated with a lidocaine infusion had a greater change in the SF-36 score (maximal at 1 week), and had a greater reduction in analgesic use (relative risk: 6.2 [95% CI: 2.24 to 17.16]), with 26.6% of patients in the lidocaine group either decreasing or stopping use of analgesics compared to 2.2% of controls. Side effects were generally mild and did not differ between the groups. The main limitation of this study is the short infusion of lidocaine.

A randomized 4-week cross-over trial by Moulin et al (2019) found no significant differences between a single infusion of lidocaine (5 mg/kg over 45 minutes) and diphenhydramine (active control) in patients (n=34) with primarily diabetic neuropathy.[15] This study is limited by the short infusion of lidocaine.

Ketamine

Three double-blind RCTs on ketamine for neuropathic pain were identified. One examined 4 days infusion in patients with CRPS,[9] the second examined 7 days infusion in patients with spinal cord injury,[16] and the third examined a single ketamine infusion in patients with mixed refractory neuropathic pain.[17]

A double-blind RCT of ketamine for CRPS was reported by Sigtermans et al (2009).[9] Sixty patients were randomized to ketamine or saline infused over 4 days. The mean ketamine infusion rate was 22 mg/h (normalized to a 70-kg patient) at the end of the treatment phase. Blood samples were collected to assess the plasma concentration of ketamine, and patients were monitored for adverse events. Two patients terminated ketamine infusion early due to psychomimetic effects (e.g., delusions, hallucinations). At baseline, NRS scores for pain were 7.2 (maximum, 10) for ketamine and 6.9 for the placebo group. The lowest pain scores (ketamine, 2.7; placebo, 5.5) were observed at the end of the first week (no patients were lost to follow-up for the primary outcome measure). Although pain scores remained statistically lower through week 11, the clinically significant difference of 2 points was maintained until week 4. None of the secondary (functional) outcome measures were improved by treatment. Moreover, 60% of patients in the placebo group correctly deduced treatment assignment (slightly better than chance); 93% of patients in the ketamine group correctly deduced treatment assignment due primarily to psychomimetic effects.

Amr (2010) published results from a double-blind, randomized, placebo-controlled study of 40 patients with neuropathic pain secondary to spinal cord injury.[16] Ketamine or saline were infused for 5 h over 7 days. All patients received gabapentin (300 mg) 3 times daily. VAS scores for pain were similar in the ketamine and saline groups at baseline (VAS of 84 of 100). During the week of infusion, VAS scores decreased more in the ketamine-infused group than in the gabapentin-only group (VAS score of 14 in the ketamine group vs. 43 in the control group at day 7). In the control group, VAS pain scores remained about the same during the 4-week follow-up. Pain scores in the ketamine-infused group increased from 14 to 22 at 1-week follow-up and remained at that level for 2 weeks after infusion. By the third week after the ketamine infusion, VAS scores had increased to 43 and were the same as the placebo-control

group. Three patients were reported to have had short-lasting delusions with ketamine infusion.

A third, small, crossover RCT conducted by Pickering et al (2020) compared a single infusion each of ketamine, ketamine/magnesium and placebo.[17] The study enrolled 20 patients with refractory neuropathic pain of mixed etiology and assessed patients 5 weeks after each crossover period. The study found no difference between groups in average daily pain intensity based on mean area under the curve (p=0.296), nor was there a difference in maximal pain (p=0.291) or nightly pain (p=0.261). The study also found no difference between interventions in any measure of function or quality of life, including Brief Pain Inventory score (p=0.527), HADS-Depression (p=0.484) or HADS-Anxiety (p=0.155) scores. There were no serious adverse events or withdrawals due to adverse events.

Tables 1 and 2 summarize the characteristics and results of selected RCTs.

Table 1. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Lidocaine						
Kim et al (2018)	South Korea	1	2015-2016	Patients had PHN or CRPS type II with an 11-point NRS score of 4 or ≥3 mo without pain relief from conservative treatment	21 patients received IV lidocaine 3 mg/kg for 4 weekly treatments of 1 h each	21 patients received IV saline for 4 weekly treatments of 1 h each
Liu et al (2018)	China	1	2015-2017	189 patients with post-herpatic neuralgia and pain > 1mo with VAS >4	A single 1 1/2 h infusion of 5 mg/kg lidocaine, injection of 1.5 mg midazolam and 3 mg granisetron, also taking pregabalin and oxycodone	1 1/2 h infusion of saline, plus midazolam and granisetron, also taking pregabalin and oxycodone
Ketamine						
Sigtermans et al (2009)	Netherlands	1	2006-2008	Patients were diagnosed with CRPS type I	30 patients randomized to ketamine infused over 4 d (titrated up to 30 mg/h for a 70-kg patient)	30 patients randomized to saline infused over 4 d
Amr	Egypt	1		40 patients with neuropathic pain secondary to spinal cord injury. Baseline mean VAS of 84	Ketamine infusion (80 mg) over a 5-hour period daily for 7 days, with gabapentin during and after infusion. (n=20)	Saline infusion over the same time period, with Gabapentin during and after infusion. (n=20)
Pickering et al (2020)	France	1	2015-2018	20 ketamine-naive patients with refractory neuropathic pain	Ketamine infusion 0.5 mg/kg over a 2-hour period	Magnesium 2 0.15g/ml ampoules over 30 mins

						Saline infusion over a 2-hour period

CRPS: complex regional pain syndrome; IV: intravenous; NRS: numeric rating scale; NR: not reported; PHN: postherpetic neuralgia

Table 2. Summary of Key Randomized Controlled Trial Results

Study	Pain Scores (SD), %	Other Clinical Outcomes	AEs
Lidocaine			
Kim et al (2018)	Vas (100 mm)		
N	42		42
Lidocaine	48.71 (40.59)		3 mild
saline	19.51 (27.27)		4 mild
p-Value	0.011		0.698
Liu et al (2018)	VAS (10 cm) at 2 weeks	SF-36 at 1 week	
N	183		
Lidocaine	2.74	80.09 (7.64)	
Placebo	2.94	30.28 (7.07)	
p-Value	NS		
Ketamine			
Sigtermans et al (2009)	11 point NRS at 1 week		
N	60		60
Ketamine	2.68 (0.51)		Nausea: 63; Vomiting: 47; Psychomimetic effects: 93; Headache: 37
Placebo	5.45 (0.48)		Nausea: 17; Vomiting: 10; Psychomimetic effects: 17; Headache: 33
p-Value		Clinically significant difference (2 points) maintained until week 4. Statistical difference maintained until week 11; at week 12, ketamine's treatment effect no longer significant (p=0.07)	Nausea: p<0.001; Vomiting: p=0.004; Psychomimetic effects: p<0.001; Headache: p=0.78
Amr et al (2010)	VAS (100 mm) at 2 weeks		
N	40		
Ketamine	22.4 (7.54)		
Placebo	44.0 (6.41)		
p-Value	p <0.01	Maintained for 2 weeks after infusion. Ketamine not significantly different from placebo at 3 and 4 weeks after infusion.	
Pickering et al (2020)	Average daily pain AUC	Brief Pain Inventory pain severity score	Any adverse even
N	20	20	20

Ketamine	196 (SD 92)	6 (SD 3)	20% (4/20)
Ketamine/Magnesium	185 (SD 100)	6 (SD 2)	35% (7/20)
Placebo	187 (SD 90)	6 (SD 2)	10% (2/20)
p-value	0.296	0.527	Not reported

AE: adverse event NRS: numeric rating scale: SD: standard deviation. AUC: area under the curve; VAS: visual analog score
[a] Measured from baseline to after the final infusion.

The purpose of the gaps tables (see Tables 3 and 4) is to display notable gaps identified in each study. The primary limitations of the RCTs are the lack of an active control for the psychomimetic effects of ketamine.

Table 3. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Kim et al (2018)			2.Did not use active placebo (diphenhydramine)		
Liu et al (2018)		4. The dose was higher and duration of treatment lower compared to other studies			
Sigtermans et al (2009)			2. Did not use an active placebo (saline)		
Amir et al (2010)			2. Did not use an active placebo (saline)		
Pickering et al (2020)				5. Pain reported as area under the curve, mean pain scores not reported	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CRPS: complex regional pain syndrome; PHN: postherpetic neuralgia.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Kim et al (2018)						
Liu et al (2018)						
Sigtermans et al (2009)						

Amir et al (2010)					1. Power calculations were not reported, but significance was obtained	2. Used a Mann-Whitney-U test rather than repeated measures analysis.
Pickering et al (2020)	3. Allocation concealment unclear				1. Power calculations were not reported	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Observational Studies

Lidocaine

A retrospective analysis by Przeklasa-Muszynska et al (2016) examined the use of 3 to 25 IV infusions of lidocaine (5 mg/kg of body weight over 30 min) in 85 patients (57% women; mean age 63 years) with neuropathic pain.[18] These disorders included: trigeminal neuralgia (n=18), chemo-induced peripheral neuropathy (n=6), PHN (n=16), diabetic neuropathy (n=7), persistent postoperative pain (n=21), and other pain syndromes, including phantom pains, mononeuropathies, compression neuropathies, central pain syndrome, CRPS, and facial neuropathy (n=17). A total of 814 infusions were delivered to 85 patients; however, treatment was discontinued in 4 patients after the first infusion due to the lack of efficacy. Assessment of pain using a numeric rating scale (NRS) ranged from 0 to 10.Efficacy increased significantly with age (71-90 years, $p<0.05$). There was a correlation between treatment efficacy and the number of infusions (6-10 infusions, $p<0.01$) and the severity of pain (NRS range, 9-10; $p<0.001$). There was no correlation between treatment efficacy and the number of years patients had experienced pain symptoms (range, 19-30 years; $p<0.05$). Reviewers reported that infusions were not interrupted due to adverse events; however, they did not report whether adverse events occurred.

Vacher et al (2022) performed a prospective case-series of 74 patients treated with a single lidocaine infusion (3 mg/kg) for chronic pain.[19,] Pain questionnaires were administered to patients at the time of infusion and again via telephone follow-up at an average of 63 days (range 30 to 240 days). The primary outcome was the change in Brief Pain Inventory (BPI) pain score. The majority of patients were female (77%). Overall, a single infusion of lidocaine did not significantly improve pain or quality of life.

Ketamine

Patil and Anitescu (2012) retrospectively analyzed data from 49 patients with severe refractory pain who had undergone 369 outpatient ketamine infusions during a 5-year period at a U.S.

academic medical center.[20] Eighteen patients were diagnosed with CRPS, and 31 had other diagnoses including refractory headache (n=8) and severe back pain (n=7). All patients exhibited signs of central sensitization. Following pretreatment with midazolam and ondansetron, ketamine infusions were administered at the highest tolerated dose for a duration ranging from 30 minutes to 8 hours. The interval between infusions ranged from 12 to 680 days (median, 233.7 days). The immediate reduction in VAS score was 7.2 for patients with CRPS and 5.1 for non-CRPS pain. Query of available patients (59%) indicated that, for 38%, pain relief lasted more than 3 weeks. Adverse events, which included confusion and hallucination, were considered minimal.

Mangnus et al (2021) performed a retrospective analysis of data from 48 adult patients with CRPS treated with ketamine infusions at a single center in the Netherlands.[21] The median duration of diagnosis was 5 years. Ketamine infusions were started at 3 mg/hour during a 7-day inpatient stay, and were increased twice daily in increments of 1 to 2 mg/hour until patients reached an effective dose. At the end of infusion and at 4 weeks post-infusion, pain score was significantly reduced from baseline (8 vs. 6; p<.001 and 8 vs. 7; p=.015, respectively). Response (decrease in pain score of ≥2 from baseline) occurred in 62% of patients at the end of infusion, but decreased to 48% at 4 weeks.

Tables 5 and 6 summarize the characteristics and results of selected observational studies.

Table 5. Summary of Key Observational Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Patil & Anitescu (2012)	Retrospective chart review	U.S.	2004-2009	Patients with CRPS, refractory headaches, or severe back pain (n=49)	Ketamine 0.5 mg/kg over 30-45 min for a total of 369 infusions	NR
Przeklasa-Muszynska (2016)	Retrospective chart review	Poland	Jan-Nov 2015	Adults with refractory neuropathic pain (n=85)	Lidocaine 5 mg/kg over 30 min once a week; range 3-25 infusions	4 weeks
Mangnus et al (2021)	Retrospective chart review	Netherlands	2010-2019	Adult patients with CRPS (n=48)	Ketamine 3mg/hour increased twice daily in increments of 1 to 2mg over 7-days	4 weeks
Vacher et al (2022)	Prospective case series	UK	2018-2020	Adults with chronic pain (N=74)	Lidocaine 3 mg/kg single infusion	Mean 63 days (range 30-240)

CRPS: complex regional pain syndrome; IV: intravenous; NR: not reported.

Table 6. Summary of Key Observational Study Results

Study	Change in Pain Score From Start of Infusion to Discontinuation	Change in Pain Score From Start of Infusion to 4	Durability	Adverse Events Patient-reported, n (%)

		weeks		
Lidocaine				
Przeklasa-Muszynska et al (2016)				
N	81		-	-
	NRS: 4.2 (SE not reported)		Not reported	Not reported
Vacher et al (2022)				
N	74			
	BPI: 6.15-5.88 (p=.106)			
Ketamine				
Patil & Anitescu (2012)				
N	49		29	49
	VAS: 5.9 (0.35)		Pain relief lasted at least 3 weeks in 38% of patients queried	23 (46.9) reported; 35 nonserious
Mangnus et al (2021)				
N	36	18		
	NRS: 2	NRS: 1		

EOT: end of treatment; VAS: visual analog scale.

Fibromyalgia

de Carvalho et al (2022) conducted a systematic review of 10 clinical trials (2 RCTs; 8 observational) evaluating lidocaine infusions in patients with fibromyalgia.[22.] A total of 461 patients were included, and the majority of patients in each study were female (95%-100%). There was a wide range of lidocaine dosage (2-7.5 mg/kg,) the number of infusions, and follow-up time-frames, which ranged from 65.7 to 90 days. Visual analog scores (in mm) ranged from 6.1 to 8.1 at baseline to 1.7 to 4.5 at short-term follow-up. In the studies evaluating long-term follow-up, VAS scores varied from 30% to 35.4%. Adverse events were variable among studies and occurred in 0% to 39.6% of cases.

One notable RCT was not included in the de Carvalho et al (2022) systematic review. Noppers et al (2011) reported on a randomized, double-blind, active placebo-controlled trial conducted in Europe using a 30-minute infusion of ketamine (n=12) or midazolam (n=12).[23.] Baseline VAS pain scores were 5.4 in the ketamine group and 5.8 in the midazolam group. At 15 minutes after termination of the infusion, significantly more patients in the ketamine group showed a reduction in VAS score for pain exceeding 50% than in the placebo group (8 vs. 3). There were no significant differences between the groups at 180 minutes after infusion (6 vs. 3), at the end of week 1 (2 vs. 0), or at the end of week 8 (2 vs. 2), all respectively. There was no difference between groups on the Fibromyalgia Impact Questionnaire scores measured weekly over 8 weeks. In this well-conducted study, a short infusion of ketamine (30 minutes) did not have a long-term analgesic effect on fibromyalgia pain.

Section Summary: IV Anesthetics for Individuals With Chronic Pain
Several RCTs have been performed using IV lidocaine or ketamine for PHN, CRPS, and diabetic neuropathy. Trials have failed to show a durable effect of lidocaine infusion on chronic pain. Two trials with a total of 100 patients provide limited evidence that courses of IV ketamine may provide temporary relief (2 to 4 weeks) to some chronic pain patients. None of the RCTs with ketamine infusion used an active control, raising the possibility of placebo effects and unblinding of patients and investigators. A systematic review specific to patients with fibromyalgia found short-term benefit with lidocaine infusions, but long-term efficacy and safety data were limited. Overall, the intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this therapy. Additional clinical trials are needed to evaluate the long-term efficacy and safety of repeat courses of IV anesthetics for chronic pain.

Treatment-Resistant Depression

Clinical Context and Therapy Purpose
The purpose of a course of IV anesthetics (e.g., lidocaine, ketamine) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with treatment-resistant depression.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with treatment-resistant depression.

Interventions
The therapy being considered is ketamine. Ketamine is approved by the U.S. Food and Drug Administration as an anesthetic, and use for psychiatric conditions is off-label. The mechanism for its effects in treatment-resistant depresion is uncertain. Ketamine is administered as an IV infusion in a medically-supervised setting.
Comparators
The following therapies are currently being used to treat psychiatric disorders: psychotropic medications and psychotherapy. Longstanding refractory depression in patients who do not benefit from treatment modification or augmentation strategies is referred to as treatment-resistant depression (TRD). The strategy for managing treatment-resistant depression generally involves modifying current antidepressant therapy or augmenting existing therapies with non-antidepressant medications (such as atypical antipsychotics). For these patients, other strategies such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, and vagus nerve stimulation techniques have also been used. Depression-focused psychotherapy may be added to pharmacotherapy, but is generally not considered stand-alone therapy for refractory depression.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and treatment-related morbidity. Commonly used scales are the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Rating Scale for Depression (HAM-D), the Patient Health Questionnaire-9 (PHQ-9), and the Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR-16).

MADRS is commonly used to evaluate the efficacy of antidepressant by assessing the severity of depression. It contains 10 items and the total score ranges from 0 to 60. The following cut-offs were proposed to classify the level of depression severity:

- 0-6: No depression (absence of symptoms)
- 7-19: Mild depression
- 20-34: Moderate depression
- 35-60: Severe depression

Hamilton Rating Scale for Depression (HAM-D)
HAM-D is a 17-item rating scale to determine the severity level of depression in a patient before, during, and after treatment. The total score ranges from 0 to 52, with the score corresponding to the following classifications:

- 0-7: No depression (normal)
- 8-16: Mild depression
- 17-23: Moderate depression
- ≥24: Severe depression

Inventory of Depressive Symptomatology–Clinician Rated 30 items

Though not completely standardized, follow-up for psychiatric disorders symptoms would typically occur in the months to years after starting treatment.

The QIDS-SR-16 is derived from the 30-item Inventory of Depressive Symptomatology and is used to rate the severity of depressive symptoms based on criterion diagnostic domains for depression, including sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance, decrease or increase in appetite or weight, and psychomotor agitation or retardation. The total score ranges from 0 to 27, with the score corresponding to the following classifications:

- 0-5: No depression
- 6-10: Mild depression
- 11-15: Moderate depression
- 16-20: Severe depression
- 21-27: Very severe depression

The PHQ-9 is a self-report on depression-related items used to monitor the severity of depression and response to treatment. Total scores correspond to these classifications:

- 0-4: None
- 5-9: Mild
- 10-14: Moderate
- 15-19: Moderately severe
- 20-27: Severe

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined for indication 1.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for double-blind RCTs;

- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.
- Studies with short-term outcomes (< 24 h) were excluded.
- Studies examining a single infusion in an inpatient setting (e.g., in conjunction with electroconvulsive therapy or emergency services for suicidal ideation) were excluded

Systematic Review

Dean et al (2021) published a systematic review of ketamine and other glutamate receptor modulators in patients with unipolar depression.[24,] Thirty-one trials were included for ketamine; however, the majority of studies investigated ketamine as a single dose, and only 7 studies were included for the response and remission outcome (n=185). While ketamine increased response and remission at 24 hours (odds ratio [OR[, 3.94; 95% CI, 1.54 to 10.10) the evidence was graded very low-certainty. In a similar analysis of patients with depression in bipolar disorder, Dean et al (2021) identified 3 trials with ketamine.[25,] Ketamine was more effective than placebo at 24 hours (odds ratio, 11.61; 95% CI, 1.25 to 107.74; p=.03); however, the evidence was deemed low-certainty and only 33 participants were included from 2 studies. Based on these analyses, evidence is lacking for efficacy beyond the acute treatment period.

Grasso et al (2024) published a systematic review on changes in cognitive outcomes in patients with unipolar TRD treated with IV ketamine infusions.26, Fourteen studies were included in the review. All included studies found reduction in depression symptoms after ketamine treatment (ranging from medium to large effect size) with no significant or long-standing adverse effects reported. Authors did note that there were several limitations in their review including the heterogeneity, small sample sizes, and limited external generalizability of populations in the included studies.

Randomized Controlled Trials

Tables 7 through 11 summarize the characteristics and results of identified RCTs. Singh et al (2016) reported an industry-sponsored phase 2 multi-center double-blind trial of ketamine (0.5 mg/kg) either 2 or 3 times per week for 4 weeks, followed by 2 weeks of open-label treatment, and then a 3 week ketamine-free phase (see Table 7).[27] Two control groups received saline infusions over the same intervals. Ketamine infusion resulted in significantly greater improvement in the MDRS compared to saline during the weeks of infusion (see Table 8). Thirty of the 33 patients in the placebo group withdrew from the study for lack of efficacy, compared to 3 of 35 who withdrew due to lack of efficacy in the ketamine groups. Although analysis was intent-to-treat with imputation of missing values, the lack of an active control and high drop-out rate are limitations of the study (see Tables 10 and 11). The most common adverse events (>20%) were headache, anxiety, dissociation, nausea, and dizziness. By the third withdrawal week, only 9 of 33 ketamine patients remained in the study with diminishing benefits shown on the MDRS. Thus, the benefit observed during the infusion phase does not appear to have been maintained after the end of infusions.

In a trial comparing ketamine infusion to ECT, Ekstrand et al (2022) randomized patients hospitalized for depression to 3 times weekly ketamine (0.5 mg/kg) or ECT in an open-label, noninferiority trial.[28] A total of 186 patients received treatment with a maximum of 12 treatment sessions. Previous treatment had included ECT in 37% of ECT recipients and 42% of ketamine recipients. Most patients were experiencing a single severe depressive episode (27% of ECT and 27% of ketamine recipients) or recurrent severe depression (34% of

ECT and 33% of ketamine) without psychotic features; 15% of ECT recipients and 19% of ketamine recipients had psychotic symptoms present, and 51% of ECT recipients and 40% of ketamine recipients had previously attempted suicide (median 2 attempts in each group). More patients achieved remission (MADRS ≤ 10) with ECT than ketamine (63% vs. 46%; OR, 0.52; 95% CI, 0.29 to 0.92). A median of 6 treatment sessions were required for remission. The authors noted that despite being inferior to ECT, ketamine is a potential treatment option for depression. Relapse rates during the 12-month follow-up were similar between treatments (70% with ketamine vs. 64% with ECT). Serious AEs were more common with ECT, but treatment-emergent AEs leading to dropout were more common with ketamine.

Anand et al (2023) reported another open-label, randomized noninferiority trial comparing ketamine (0.5 mg/kg 3 times weekly) with ECT (3 times weekly) in adults with treatment-resistant moderate or severe depression (lack of response to ≥2 adequate trials of antidepressant therapy and MADRS score >20).[29] Participants were patients experiencing depressive episodes with psychotic features were excluded. Among 403 randomized patients, most (89.1%) were outpatient at the time of randomization. Previous treatment had included ECT and/or ketamine in 11.5% and 7% of ketamine recipients and 10.3% and 3.9% of ECT recipients, respectively. Suicide had previously been attempted in 36.5% of ketamine recipients and 41.4% of ECT recipients. In the primary analysis, 55.4% of participants assigned to ketamine and 41.2% of participants assigned to ECT experienced a response (≥50% reduction in QIDS-SR-16 score from baseline) after 3 weeks (p<.001 for noninferiority). Among participants who achieved an initial response, relapse (QIDS-SR-16 score >12) occurred in 19% of ketamine and 35.4% of ECT recipients at 1-month follow-up and 34.5% of ketamine and 56.3% of ECT recipients at 6-month follow-up. Patient-reported memory function scores were higher in the ketamine group than the ECT group, and fewer patients in the ketamine group reported cognitive symptoms. Patients in both groups experienced similar improvements in quality-of-life scores. Moderate or severe adverse events were reported in 25.1% of ketamine recipients and 32.4% of ECT recipients; individual events occurred at similar rates with the exception of muscle pain or weakness, which was reported in 0.5% of ketamine recipients and 5.3% of ECT recipients (p=.01).

Table 7. Summary of Key RCT Characteristics

Study	Design	Countries	Sites	Dates	Participants	Interventions	
						Active	**Comparator**
Singh et al (2016)	Double-blind phase 2	US	14	2012-2013	68 patients with TRD a score ≥ 34 on the IDS-CR	I.V. ketamine (0.5 mg/kg for 40 min), either 2 (n=18) or 3 (n=17) times a week for 4 weeks, followed by 2 weeks of open-label and then a 3 week ketamine-free phase	Saline infusion either 2 (n=17) or 3 (n=16) times per week over the same interval.
Ekstrand et al (2022)	Open-label, noninferiority RCT	Sweden	6	NR	186 adult inpatients with depression	IV ketamine 0.5 mg/kg 3 times weekly up to 12 treatments	ECT
Anand et al (2023)	Open-label, noninferiority	U.S.	5	2017-2022	403 adults with TRD	IV ketamine 0.5 mg/kg twice weekly	ECT 3 times weekly for 3

	RCT				and a score >20 on the MADRS	for 3 weeks	weeks

IDS-CR: Inventory of Depressive Symptomatology–Clinician Rated; RCT: randomized controlled trial; TRD: treatment-resistant depression

Table 8. Summary of Key RCT Results

Study	YBOCS Response to Day 7[1], n (%)	Change in MADRS to Day 15, Mean (SD)	Change in MADRS to Day 29, Mean (SD)	Remitters (MADRS <10) , n (%)	Drug-related Adverse Events, n (%)	Change in CAPS-5 at Day 15, Mean (SD)	Response (≥50% reduction in QIDS-SR-16 score from baseline) after 3 weeks, n (%)
Singh et al (2016)							
N		67 ITT	67 ITT	58	68		
Ketamine 2		-18.4 (12)	-21.2 (12.9)	6 (37.5)	13 (72.2)		
Ketamine 3		-17.7 (7.3)	-21.1 (11.2)	3 (23.1)	10 (58.8)		
Saline 2		-5.7 (10.2)	-4.0 (9.1)	1 (7.7)	6 (37.5)		
Saline 3		-3.1 (5.7)	-3.6 (6.6)	0 (0)	5 (31.3)		
p-Value		<.001	NR	NS			
Feder et al (2021)							
Ketamine						NR	
Midazolam						NR	
Difference (p value)						-11.88 (.004)	
Ekstrand et al (2022)							
N				186			
Ketamine				44 (46)			
ECT				57 (63)			
OR (95% CI)				0.51 (0.29 to 0.92)			
Anand et al (2023)							
N							
Ketamine				74 (37.9)			108 (55.4)
ECT				37 (21.8)			70 (41.2)
Difference, % (95% CI)				16.2 (7.0 to 25.4)			14.2 (3.9 to 24.2)

p-value for noninferiority				--			<.001

CAPS-5: Clinician-Administered PTSD Scale for DSM-5; CI: confidence interval; ECT: electroconvulsive therapy; ITT: intent to treat; MADRS: Montgomery-Asberg Depression Rating Scale; NR: not reported; OR: odds ratio; NS: not significant; QIDS-SR-16: 16-item Quick Inventory of Depressive Symptomatology - Self-Report; SD: standard deviation; YBOCS: Yale-Brown Obsessive-Compulsive Scale.
[1]YBOCS reduction ≥35%.

Trials that have found no benefit of ketamine infusion are described in Table 9. Ionescu et al (2019) reported a double-blind trial in 26 patients with chronic and current suicidal ideation.[30] The study found no significant difference in HAM-D between the saline and ketamine groups at the end of infusion (6 infusions over 3 weeks) or after 3 months of follow-up. Limitations of the study included possible insufficient power due to difficulties in recruitment and a high drop-out rate (see Tables 10 and 11). Review of clinicaltrials.gov shows a large number of small studies that have not been published or followed with larger trials.

Table 9. RCTs with Negative Results

Study	Countries	Sites	Dates	Design	Participants	Interventions		Outcome Measure	Follow-Up	Comment
						Active	**Comparator**			
Ionescu et al (2019)	US	1	2013-2015	Double-Blind	26 medicated patients with chronic and current suicidal ideation	Six ketamine infusions (0.5 mg/kg for 45 min) over 3 weeks	Saline at the same schedule	HAM-D	End of infusion and at 3 mo after infusion	No significant difference in HAM-D between groups at the end of infusion. 2 patients in each group were in remission at 3 mo follow-up.

RCT: randomized controlled trial

Table 10. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Ionescu (2019)			2. Did not use an active placebo (saline)		1. Follow-up was performed at 3 mo, but not earlier time points
Singh et al (2016)			2. Did not use an active placebo (saline)		

Ekstrand et al (2022)					
Anand et al (2023)					

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 11. Study Design and Conduct limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Ionescu (2019)				1. Only 14 of 26 patients completed the study	1. Power calculations were not reported	
Singh et al (2016)				1. 91% of patients in the control group withdrew due to lack of efficacy. Only 27% of ketamine patients remained in the study at the end of the withdrawal phase		
Ekstrand et al (2022)		1. Open-label				
Anand et al (2023)		1. Open-label				

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Observational Studies

Numerous observational studies have evaluated ketamine in psychiatric disorders and selected studies are summarized in Tables 12 and 13.[31-35] Ketamine has generally been found to be effective for depression, suicidality, and OCD in these observations; however, the inherent limitations of observational study design prohibit firm conclusions regarding the effectiveness and safety of ketamine infusions.

Table 12. Summary of Key Case Series Characteristics

Study	Country	Participants	Treatment Delivery	Follow-Up

McInnes et al (2022)	U.S.	537 patients with depression	Ketamine 4-8 infusions over 7-28 days	14-31 days after final infusion
Oliver et al (2022)	U.S.	424 patients with treatment-resistant depression or suicidal ideation	Ketamine 0.5 mg/kg for 6 infusions followed by as needed booster infusions thereafter	Up to 52 weeks
Zhou et al (2022)	China	111 patients with treatment-resistant depression	Ketamine 0.5 mg 3 times weekly for a total of 6 doses	26 days
Pfeiffer et al (2024)	U.S	215 patients with depression	Ketamine infusion (mean dose 59 mg); mean total number of infusions was 18	up to 12 months
Gutierrez et al (2024)	Canada	71 patients with treatment-resistant depression	IV low dose ketamine (f 0.5 mg/kg) bi-weekly sessions for 4 weeks	4 weeks

OCD: obsessive-compulsive disorder; SRI: serotonin reuptake inhibitor.

Table 13. Summary of Key Case Series Results

Study	Treatment	Change From Baseline	Response , n (%)	Partial Response , n (%)	Remission, n (%)
Sharma et al (2020)	Ketamine	YBOCS: 31.4 vs. 26.9; p=.01	YBOCS: 1 (7.1)[a]	YBOCS: 2 (14.3)[b]	
McInnes et al (2022)	Ketamine	PHQ-9: 8.7 (SD, 6.6; 95% CI, 8.1-9.2)	288 (53.6)		155 (28.9)
Oliver et al (2022)	Ketamine	Mean PHQ scores significantly decreased after week 1 (p<.001; results reported graphically)	50% of patients had responded by day 36		20% were in remission by 30 days
Zhou et al (2022)	Ketamine	MADRS: baseline 32.1 to 15.7 at follow-up; p<.001			
Pfeiffer et al (2024	Ketamine	Mean improvement in PHQ9 scores at weeks 6, 12, and 26: mean improvement in PHQ-9 scores was 4.6 (SD = 6.8), 4.4 (SD = 6.5), and 4.7 (SD = 6.7) respectively	At week 6, 26% had a 50% improvement in PHQ-9 score		At week 6, 5% had PHQ-9 score ≤ 5

Gutierrez et al (2024)	Ketamine	BDI-II and MADRS: statistically significant reduction in SI comparing the baseline to treatment endpoint scores	CGI-S scale: 54.93% of patients responded to treatment	CGI-S scale: 23.94% achieved remission	CGI-S scale: 23.94% achieved remission

YBOCS:Yale-Brown Obsessive-Compulsive Scale.
1YBOCS reduction ≥35%.
1YBOCS reduction 25% to 35%.

Section Summary: Intravenous Anesthetics for Patients With TRD
Two double-blind trials have been published that compared multiple ketamine infusions with saline for TRD. There is a possibility of publication bias due to the lack of publication of many other small trials. Systematic reviews in unipolar depression and depression in patients with bipolar disorder have identified numerous studies evaluating ketamine infusion. However, the studies are generally limited to a single ketamine infusion. One study with 26 patients found no significant difference in a depression scale at the end of infusion. A larger RCT (N=68) found a significantly greater improvement in a depression scale during the 4-week infusion period, but the effect diminished over 3 weeks post-infusion. The trial did not use an active control, raising the possibility of placebo effects and unblinding of patients and investigators. An RCT comparing ketamine infusion to ECT in hospitalized patients with depression found improved remission rates with ECT, whereas another RCT comparing ketamine infusion with ECT in a predominantly outpatient, less severely ill sample found that ketamine was noninferior to ECT in inducing response with numerical improvements in quality of life and adverse effects. Multiple observational studies have demonstrated efficacy of ketamine infusions in depression, but limited conclusions can be made based on the observational study design. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. The intense treatment protocols, the severity of adverse events, and the short treatment durability limit the clinical utility of the treatment. High-quality clinical trials, several of which are in progress, are needed to evaluate the long-term safety and efficacy of IV ketamine use for depression.

Other Psychiatric Disorders
Clinical Context and Therapy Purpose
The purpose of a course of IV anesthetics (e.g., lidocaine, ketamine) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with other psychiatric disorders (e.g., depression,obsessive-compulsive disorder [OCD], post-traumatic stress disorder [PTSD]).

Populations
The relevant population of interest is individuals with psychiatric disorders (e.g., OCD, PTSD).

Interventions
The therapy being considered is ketamine. Ketamine is approved by the U.S. Food and Drug Administration as an anesthetic, and use for psychiatric conditions is off-label. The mechanism for its effects in psychiatric disorders is uncertain. Ketamine is administered as an IV infusion in a medically-supervised setting.

Comparators
The following therapies are currently being used to treat psychiatric disorders: psychotropic medications and psychotherapy.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and treatment-related morbidity. Commonly used scales are the Clinically Administered Post-Traumatic Stress Disorder (PTSD) Scale (CAPS-5), and the Yale-Brown Obsessive-Compulsive Scale (YBOCS).

The CAPS-5 is the gold standard in assessment of PTSD symptoms. The CAPS-5 is a structured interview performed by clinicians or researchers that is used to diagnose PTSD and assess PTSD symptoms. Scores for each item range from 0 (absent) to 4 (extreme/incapacitating); total scores range from 0 to 120.

The YBOCS is a 10-item clinician-administered scale that is the most widely used rating scale for OCD. The YBOCS rates 5 dimensions related to obsessions and compulsions: time spent or occupied; interference with functioning or relationships; degree of distress; resistance; and control (i.e., success in resistance). Each item is scored on a 4-point scale with 0 representing no symptoms and 4 representing extreme symptoms. Total scores of the YBOCS correspond to the following indicated classifications:

- 0-7: Subclinical
- 8-15: Mild
- 16-23: Moderate
- 24-31: Severe
- 32-40: Extreme

Randomized Controlled Trials
Tables 14 through 17 summarize the characteristics and results of identified RCTs. Rodriguez et al (2013) performed a double-blind, placebo-controlled trial in patients with serotonin reuptake inhibitor (SRI)-resistant OCD to compare the effects of ketamine (0.5 mg/kg given over 40 minutes on 2 occasions at least 1 week apart) with saline placebo.[36] Patients had failed or refused treatment with at least 1 trial of SRI therapy and/or cognitive behavioral therapy. The mean age of patients was 34.2 years and the mean YBOCS score was 28.2. A significant carryover effect was detected with ketamine, and these patients did not return to their baseline disease severity; therefore, data from each phase of the crossover trial were not combined and results were presented only for the first-phase data (ketamine first [n=8] and saline first [n=7]). A higher proportion of patients treated with ketamine achieved treatment response (≥35% reduction in YBOCS score; 50% vs. 0%; p<.05). The authors noted the small sample size and unblinding due to adverse effects of ketamine.

Feder et al (2021) performed a double-blind trial comparing IV ketamine with IV midazolam, each administered 3 times weekly over 2 weeks, in adult patients with PTSD.[37] The primary outcome measure was change in PTSD symptom severity, assessed using the CAPS-5, from baseline to 2 weeks. The mean duration of PTSD was 14.9 years. Thirteen (43.3%) patients were receiving concomitant psychotropic medications, and 17 (56.7%) were receiving concomitant psychotherapy. At week 2, the mean CAPS-5 total score was lower in the ketamine group compared to the midazolam group (difference, 11.88 points; p=.004). The

most common adverse events that occurred more frequently with ketamine included nausea or vomiting (33% vs. 20%), headache (33% vs. 20%), and fatigue (20% vs. 7%). The authors noted the potential for unblinding in the ketamine group due to the higher rate of dissociative symptoms.

Table 14. Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	Design	Countries	Sites	Dates	Participants	Interventions	
						Active	Comparator
Rodriguez et al (2013)	Double-blind, crossover RCT	U.S.	1	2010-2012	15 adult patients with SRI-resistant OCD and near-constant obsessions	IV ketamine (0.5 mg/kg) given over 40 min on 2 occasions at least 1 week apart	Saline infusion given over 40 min on 2 occasions at least 1 week apar
Feder et al (2021)	Double-blind RCT	U.S.	1	2015-2020	30 adult patients with chronic PTSD	IV ketamine 0.5 mg/kg 3 times per week over 2 consecutive weeks	IV midazolam 0.045 mg/kg 3 times per week over 2 consecutive weeks

NR: not reported; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; RCT: randomized controlled trial; SRI: serotonin reuptake inhibitor;

Table 15. Summary of Key Randomized Controlled Trial Results

Study	YBOCS Response to Day 7[1], n (%)	Change in MADRS to Day 15, Mean (SD)	Change in MADRS to Day 29, Mean (SD)	Remitters (MADRS <10) , n (%)	Drug-related Adverse Events, n (%)	Change in CAPS-5 at Day 15, Mean (SD)	Response (≥50% reduction in QIDS-SR-16 score from baseline) after 3 weeks, n (%)
Rodriguez et al (2013)							
N	15						
Ketamine	7 (50)						
Placebo	0						
Feder et al (2021)							
Ketamine						NR	
Midazolam						NR	
Difference (p value)						-11.88 (.004)	

CAPS-5: Clinician-Administered PTSD Scale for DSM-5; CI: confidence interval; ITT: intent to treat; NR: not reported; OR: odds ratio; NS: not significant;

Table 16. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Rodriguez et al (2013),					1. Follow-up only performed up to 1 week
Feder et al (2021)					1. Follow-up only performed up to 2 weeks

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 17. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Rodriguez et al (2013)		1. Potential unblinding due to dissociative effects of ketamine				4. Data from second phase of crossover not included due to carryover effect of ketamine
Feder et al (2021)		1. Potential unblinding due to dissociative effects of ketamine				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Observational Studies

Observational studies have evaluated ketamine in psychiatric disorders and selected studies are summarized in Tables 18 and 19. Ketamine has generally been found to be effective for OCD in these observations; however, the inherent limitations of observational study design prohibit firm conclusions regarding the effectiveness and safety of ketamine infusions.

Table 18. Summary of Key Observational Study Characteristics

Study	Country	Participants	Treatment Delivery	Follow-Up
Sharma et al (2020)	India	14 patients with SRI-resistant OCD	Ketamine 0.5 mg/kg over 40 min either	2-3 weeks

			twice weekly or 3 times weekly	

OCD: obsessive-compulsive disorder; SRI: serotonin reuptake inhibitor.

Table 19. Summary of Key Observational Study Results

Study	Treatment	Change From Baseline	Response , n (%)	Partial Response , n (%)	Remission, n (%)
Sharma et al (2020)[38]	Ketamine	YBOCS: 31.4 vs. 26.9; p=.01	YBOCS: 1 (7.1)[a]	YBOCS: 2 (14.3)[b]	

CI: confidence interval; MADRS: Montgomery-Asberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation; YBOCS: Yale-Brown Obsessive-Compulsive Scale.
[a] YBOCS reduction ≥35%.
[b] YBOCS reduction 25% to 35%.

Section Summary: Intravenous Anesthetics for Patients With Other Psychiatric Disorders

One double-blind placebo-controlled trial and case series were identified in OCD, and 1 double-blind trial was identified that compared multiple ketamine infusions with midazolam in chronic PTSD. There is a possibility of publication bias due to the lack of publication of many other small trials. One double-blind, crossover RCT in patients with SRI-resistant OCD found that ketamine infusion provided higher frequency of YBOCS response at day 7 compared to placebo; however, unblinding was suspected and only data from the first phase were analyzed because of a carryover effect of ketamine. A case series also found significant improvements in YBOCS at 2 to 3 weeks, but only 1 patient demonstrated YBOCS response. A single RCT in patients with chronic PTSD (N=30) found that ketamine infusion produced significantly greater improvements in a PTSD symptom scale at 2 weeks compared to midazolam. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. The intense treatment protocols, the severity of adverse events, and the short limited treatment durability limit the clinical utility of the treatment. Raise questions about the net health benefit of this therapy. High-quality clinical trials, several of which are in progress, are needed to evaluate the long-term safety and efficacy of IV ketamine for psychiatric disorders.

SUMMARY OF EVIDENCE

For individuals who have chronic pain syndromes (e.g., CRPS, fibromyalgia, headache, neuropathic pain, spinal cord injury) who receive IV anesthetics (e.g., lidocaine, ketamine), the evidence includes several randomized controlled trials. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. Several RCTs have been performed using intravenous lidocaine or ketamine for postherpetic neuralgia (PHN), CRPS, and diabetic neuropathy. Trials have failed to show a durable effect of lidocaine infusion on chronic pain. Two trials with a total of 100 patients provide limited evidence that courses of IV ketamine may provide temporary relief (2 to 4 weeks) to some chronic pain patients. Neither of the RCTs with ketamine infusion used an active control, raising the possibility of placebo effects. A third trial found no benefit of a single infusion of ketamine or ketamine/magnesium. Overall, the intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this procedure. Additional clinical trials are needed to evaluate the long-term efficacy and safety of repeat courses of IV anesthetics for chronic pain. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have treatment-resistant depression who receive a course of IV ketamine, the evidence consists of systematic reviews, RCTs, and case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. Two publications of double-blind trials were identified that compared repeated ketamine infusion with an infusion of saline for treatment-resistant depression. Additionally, 2 open-label randomized trials comparing ketamine infusion to electroconvulsive therapy (ECT) were identified. There is a possibility of publication bias due to the lack of publication of many other small trials. Systematic reviews in patients with unipolar depression or depression related to bipolar disorder have identified numerous studies evaluating the efficacy of ketamine infusion. While the analyses indicate depression improvement in the short-term, there is limited evidence beyond a single infusion. One study with 26 patients found no significant difference in a depression scale at the end of infusion. A larger RCT (N=68) found a significantly greater improvement in a depression scale during the 4-week infusion period, but the effect diminished over 3 weeks post-infusion. The trial did not use an active control, raising the possibility of placebo effects and unblinding of patients and investigators. The open-label randomized trials comparing ketamine with ECT produced mixed results, with the first trial indicating ketamine was not noninferior to ECT in inducing remission and the second trial indicating ketamine was noninferior to ECT in inducing response. These divergent findings may be attributable to differences in the populations studied, as the first trial was conducted in severely ill inpatients and the second trial was conducted in a less severely ill, predominantly outpatient sample. Large observational studies in patients with depression indicate improvement on depression rating scales following ketamine infusions; however, these studies lack a control group, and no firm conclusions on the effectiveness or safety of serial ketamine infusions can be drawn from this evidence. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. The intense treatment protocols, the severity of adverse events, and the short treatment durability limit the clinical utility of the treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other psychiatric disorders (e.g., obsessive-compulsive disorder [OCD], post-traumatic stress disorder [PTSD]) who receive a course of IV ketamine, the evidence consists of RCTs and case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. One double-blind placebo-controlled trial and case series for OCD treatment, and 1 double-blind trial comparing multiple ketamine infusions with midazolam in chronic PTSD were identified. There is a possibility of publication bias due to the lack of publication of many other small trials. One double-blind, crossover RCT in patients with serotonin reuptake inhibitor (SRI)-resistant OCD (N=15) found that ketamine infusion provided a higher frequency of Yale-Brown Obsessive Compulsive Scale (YBOCS) response at day 7 compared with placebo; however, unblinding was suspected and only data from the first phase were analyzed because of a carryover effect of ketamine. A case series (N=14) identified only 1 patient who demonstrated prespecified significant YBOCS response after 2 to 3 weeks. A single RCT in patients with chronic PTSD (N=30) found that ketamine infusion produced significantly greater improvements in a PTSD symptom scale at 2 weeks compared to midazolam. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. The intense treatment protocols, the severity of adverse events, and the short treatment durability limit the clinically utility of treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society of Regional Anesthesia and Pain Medicine et al

In 2018, the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine and the American Society of Anesthesiologists issued a joint consensus guideline on the use of intravenous ketamine for treatment of chronic pain.[39] The guideline found:

- Weak evidence supporting use of IV ketamine for short-term improvement in patients with spinal cord injury pain
- Moderate evidence supporting use of IV ketamine for improvement in patients with CRPS up to 12 weeks
- Weak or no evidence for immediate improvement with IV ketamine use for other pain conditions, including mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache and spinal pain

American Psychiatric Association

In 2017, the American Psychiatric Association published an evidence review and consensus opinion of the use of ketamine in treatment-resistant depression.[40] The Association noted that "while ketamine may be beneficial to some patients with mood disorders, it is important to consider the limitations of the available data and the potential risk associated with the drug when considering the treatment option."

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12.

Table 11. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05339074	Maintenance Ketamine Infusions for Treatment-Resistant Bipolar Depression: An Open-Label Extension Trial	60	Feb 2026
NCT05045378	Low-dose Ketamine Infusion Among Adolescents With Treatment-resistant Depression: a Randomized, Double-blind Placebo-control Study	54	Dec 2026
NCT03674671	Investigations on the Efficacy of Ketamine in Depression in Comparison to Electroconvulsive Therapy	240	Dec 2025
NCT05973851	A Randomised, Controlled Trial to Investigate the Effect of a Four Week Intensified Pharmacological Treatment for Major Depressive Disorder Compared to Treatment as Usual in Subjects Who Had a First-time Treatment Failure on Their First-line Treatment	418	Jun 2026
NCT06034821	Rapid Reversal of Suicidal Depression: Comparative Effectiveness of ECT vs. KETAMINE Over the Lifespan (REaKT-SD)	1500	Mar 2030
Unpublished			

NCT02556606	Ketamine for Treatment-Resistant Late-Life Depression	72	Mar 2021
NCT05168735	Ketamine + Mindfulness for Depression	43	Sep 2023
NCT02461927	Ketamine for The Rapid Treatment of Major Depression and Alcohol Use Disorder	65	Oct 2023

NCT: national clinical trial

Government Regulations

National:

No national coverage determination.

Local:

No local coverage determination.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Monitored Anesthesia
- Dental General Anesthesia

References

1. Yousefshahi F, Predescu O, Francisco Asenjo J. The Efficacy of Systemic Lidocaine in the Management of Chronic Pain: A Literature Review. Anesth Pain Med. Jun 2017; 7(3): e44732. PMID 28856112
2. Israel JE, St Pierre S, Ellis E, et al. Ketamine for the Treatment of Chronic Pain: A Comprehensive Review. Health Psychol Res. 2021; 9(1): 25535. PMID 34746491
3. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. Jan 2018; 38(1): 1-211. PMID 29368949
4. Gwathmey KG, Pearson KT. Diagnosis and management of sensory polyneuropathy. BMJ. May 08 2019; 365: l1108. PMID 31068323
5. Winslow BT, Vandal C, Dang L. Fibromyalgia: Diagnosis and Management. Am Fam Physician. Feb 2023; 107(2): 137-144. PMID 36791450
6. McIntyre RS, Alsuwaidan M, Baune BT, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry. Oct 2023; 22(3): 394-412. PMID 37713549
7. Wertli MM, Kessels AG, Perez RS, et al. Rational pain management in complex regional pain syndrome 1 (CRPS 1)--a network meta-analysis. Pain Med. Sep 2014; 15(9): 1575-89. PMID 25234478

8. Schwartzman RJ, Alexander GM, Grothusen JR, et al. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain. Dec 15 2009; 147(1-3): 107-15. PMID 19783371
9. Sigtermans MJ, van Hilten JJ, Bauer MCR, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain. Oct 2009; 145(3): 304-311. PMID 19604642
10. O'Connell NE, Wand BM, McAuley J, et al. Interventions for treating pain and disability in adults with complex regional pain syndrome. Cochrane Database Syst Rev. Apr 30 2013; 2013(4): CD009416. PMID 23633371
11. Ferraro MC, Cashin AG, Wand BM, et al. Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews. Cochrane Database Syst Rev. Jun 12 2023; 6(6): CD009416. PMID 37306570
12. Lee JH, Koutalianos EP, Leimer EM, et al. Intravenous Lidocaine in Chronic Neuropathic Pain: A Systematic Review. Clin J Pain. Dec 01 2022; 38(12): 739-748. PMID 36288104
13. Kim YC, Castañeda AM, Lee CS, et al. Efficacy and Safety of Lidocaine Infusion Treatment for Neuropathic Pain: A Randomized, Double-Blind, and Placebo-Controlled Study. Reg Anesth Pain Med. May 2018; 43(4): 415-424. PMID 29381569
14. Liu H, Lu F, Zhou D, et al. The Analgesic and Emotional Response to Intravenous Lidocaine Infusion in the Treatment of Postherpetic Neuralgia: A Randomized, Double-Blinded, Placebo-controlled Study. Clin J Pain. Nov 2018; 34(11): 1025-1031. PMID 29698250
15. Moulin DE, Morley-Forster PK, Pirani Z, et al. Intravenous lidocaine in the management of chronic peripheral neuropathic pain: a randomized-controlled trial. Can J Anaesth. Jul 2019; 66(7): 820-827. PMID 31098961
16. Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial. Pain Physician. 2010; 13(3): 245-9. PMID 20495588
17. Pickering G, Pereira B, Morel V, et al. Ketamine and Magnesium for Refractory Neuropathic Pain: A Randomized, Double-blind, Crossover Trial. Anesthesiology. Jul 2020; 133(1): 154-164. PMID 32384291
18. Przeklasa-Muszyńska A, Kocot-Kępska M, Dobrogowski J, et al. Intravenous lidocaine infusions in a multidirectional model of treatment of neuropathic pain patients. Pharmacol Rep. Oct 2016; 68(5): 1069-75. PMID 27552062
19. Vacher E, Kosela M, Song-Smith C, et al. Lidocaine infusions in chronic pain management: A prospective case series analysis. Br J Pain. Jun 2022; 16(3): 270-280. PMID 35646339
20. Patil S, Anitescu M. Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: a 5-year retrospective analysis. Pain Med. Feb 2012; 13(2): 263-9. PMID 21939497
21. Mangnus TJP, Dirckx M, Bharwani KD, et al. Effect of intravenous low-dose S-ketamine on pain in patients with Complex Regional Pain Syndrome: A retrospective cohort study. Pain Pract. Nov 2021; 21(8): 890-897. PMID 34233070
22. de Carvalho JF, Skare TL. Lidocaine in fibromyalgia: A systematic review. World J Psychiatry. Apr 19 2022; 12(4): 615-622. PMID 35582338
23. Noppers I, Niesters M, Swartjes M, et al. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. Eur J Pain. Oct 2011; 15(9): 942-9. PMID 21482474
24. Dean RL, Hurducas C, Hawton K, et al. Ketamine and other glutamate receptor modulators for depression in adults with unipolar major depressive disorder. Cochrane Database Syst Rev. Sep 12 2021; 9(9): CD011612. PMID 34510411

25. Dean RL, Marquardt T, Hurducas C, et al. Ketamine and other glutamate receptor modulators for depression in adults with bipolar disorder. Cochrane Database Syst Rev. Oct 08 2021; 10(10): CD011611. PMID 34623633
26. Grasso V, Gutierrez G, Alzbeidi N, et al. Cognitive changes in patients with unipolar TRD treated with IV ketamine: A systematic review. Prog Neuropsychopharmacol Biol Psychiatry. Dec 20 2024; 135: 111095. PMID 39032855
27. Singh JB, Fedgchin M, Daly EJ, et al. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. Am J Psychiatry. Aug 01 2016; 173(8): 816-26. PMID 27056608
28. Ekstrand J, Fattah C, Persson M, et al. Racemic Ketamine as an Alternative to Electroconvulsive Therapy for Unipolar Depression: A Randomized, Open-Label, Non-Inferiority Trial (KetECT). Int J Neuropsychopharmacol. May 27 2022; 25(5): 339-349. PMID 35020871
29. Anand A, Mathew SJ, Sanacora G, et al. Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. N Engl J Med. Jun 22 2023; 388(25): 2315-2325. PMID 37224232
30. Ionescu DF, Bentley KH, Eikermann M, et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: A randomized, double blind, placebo controlled trial. J Affect Disord. Jan 15 2019; 243: 516-524. PMID 30286416
31. McInnes LA, Qian JJ, Gargeya RS, et al. A retrospective analysis of ketamine intravenous therapy for depression in real-world care settings. J Affect Disord. Mar 15 2022; 301: 486-495. PMID 35027209
32. Oliver PA, Snyder AD, Feinn R, et al. Clinical Effectiveness of Intravenous Racemic Ketamine Infusions in a Large Community Sample of Patients With Treatment-Resistant Depression, Suicidal Ideation, and Generalized Anxiety Symptoms: A Retrospective Chart Review. J Clin Psychiatry. Sep 12 2022; 83(6). PMID 36112599
33. Zhou Y, Wang C, Lan X, et al. The effectiveness of repeated intravenous ketamine on subjective and objective psychosocial function in patients with treatment-resistant depression and suicidal ideation. J Affect Disord. May 01 2022; 304: 78-84. PMID 35176337
34. Pfeiffer PN, Geller J, Ganoczy D, et al. Clinical Outcomes of Intravenous Ketamine Treatment for Depression in the VA Health System. J Clin Psychiatry. Jan 08 2024; 85(1). PMID 38206011
35. Gutierrez G, Kang MJY, Vazquez G. IV low dose ketamine infusions for treatment resistant depression: Results from a five-year study at a free public clinic in an academic hospital. Psychiatry Res. May 2024; 335: 115865. PMID 38518518
36. Rodriguez CI, Kegeles LS, Levinson A, et al. Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. Neuropsychopharmacology. Nov 2013; 38(12): 2475-83. PMID 23783065
37. Feder A, Costi S, Rutter SB, et al. A Randomized Controlled Trial of Repeated Ketamine Administration for Chronic Posttraumatic Stress Disorder. Am J Psychiatry. Feb 01 2021; 178(2): 193-202. PMID 33397139
38. Sharma LP, Thamby A, Balachander S, et al. Clinical utility of repeated intravenous ketamine treatment for resistant obsessive-compulsive disorder. Asian J Psychiatr. Aug 2020; 52: 102183. PMID 32554207
39. Cohen SP, Bhatia A, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the

American Society of Anesthesiologists. Reg Anesth Pain Med. Jul 2018; 43(5): 521-546. PMID 29870458
40. Sanacora G, Frye MA, McDonald W, et al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. JAMA Psychiatry. Apr 01 2017; 74(4): 399-405. PMID 28249076
41. Peyrovian B, McIntyre RS, Phan L, et al. Registered clinical trials investigating ketamine for psychiatric disorders. J Psychiatr Res. Aug 2020; 127: 1-12. PMID 32315806
42. Blue Cross Blue Shield Association. Intravenous Anesthetics for the Treatment of Chronic Pain. Medical Policy Reference Manual. MPRM 5.01.16. Last updated November 2024.
43. Hayes Clinical Research Response. Intravenous Ketamine for Treatment of Migraine Headache. Lansdale, PA: HAYES, Inc., published July 2017. Archived August 2018.
44. HAYES Health Technology Brief. Intravenous Ketamine for Chronic Nonmalignant Pain. Lansdale, PA: HAYES, Inc., published April 2015, updated March 2017. Archived May 2018.

45. HAYES Directory. Intravenous Lidocaine Infusion for Neuropathic Pain: A review of reviews. Lansdale, PA: HAYES, Inc., published April 2017. Archived May 2019.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/18	12/12/17	12/12/17	Joint policy established
3/1/19	12/11/18		Routine policy maintenance, updated rationale, added reference # 8. No changes in policy status.
3/1/20	12/17/19		Rationale reformatted, reference # 8 deleted and references # 35-39 added. Title changed to “Intravenous Anesthetics for the treatment of Chronic Pain and Psychiatric Disorders.” No change in policy status.
3/1/21	12/15/20		Rationale updated, reference 9 and 19 added. No change in policy status. Outdated references deleted.
3/1/22	12/14/21		Updated rationale, added references, no change in policy status.
3/1/23	12/20/22		Routine policy maintenance, no change in policy status.
3/1/24	12/19/23		Updated rationale, added references 11, 12, 19, 22, 24, 25, 30, 33-35. No change in policy status. Vendor managed: N/A (ds)
3/1/25			MPS divided into two parts, rationale updated references 26, 34, 35 added. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2026

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE POLICY: INTRAVENOUS ANESTHETICS FOR THE TREATMENT OF CHRONIC PAIN AND PSYCHIATRIC DISORDERS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.